Loss of Bronchoprotection With Salmeterol

To the Editor:

I read with considerable interest the report by Bhagat et al (CHEST 1995; 105:1235-39) in which they describe a “Rapid Onset of Tolerance to the Bronchoprotective Effect of Salmeterol.” They suggest that their findings reinforce the notion that β2-agonists as regular therapy should be used with caution.

Airway hyperresponsiveness appears to be an important characteristic of asthma, and it may be related to the severity of asthma symptoms. The finding of a reduction in bronchoprotective effect against methacholine with salmeterol use (CHEST 1995; 105:1235-39) is not easily explained. Furthermore, the clinical significance of these findings in terms of patient management has not been clarified to date. Like the study of Bhagat et al, many of the reports1-3 describing a reduction in bronchoprotection with regular β2-agonist use included mild asthmatics who were not using regular antiinflammatory medication (either steroid or nonsteroid). At the present time, salmeterol is not recommended for use in patients who are not receiving optimal antiinflammatory therapy. Booth et al4 studied mild-to-moderate asthmas receiving maintenance inhaled corticosteroids and found that salmeterol provided significant protection against methacholine-induced bronchoconstriction with no significant attenuation of bronchoprotection with 8 weeks of regular use. Furthermore, there are data5 that suggest that salmeterol use is not associated with any “proinflammatory” effect as reflected by changes in inflammatory cell numbers or activation in bronchoalveolar lavage fluid of asthmatics receiving maintenance-inhaled corticosteroids.

Recently, I have become increasingly concerned about the many patients who present to the clinic indicating that they are reluctant to use their short-acting β2-agonists (even infrequently) because of the media reports about possible harmful effects with regular use. Given the controversy that exists regarding the potential adverse effects associated with regular use of short-acting β2-agonists, it is important that we continue to keep patients informed about appropriate treatment strategies, including the use of long-acting β2-agonists in conjunction with appropriate antiinflammatory therapy. Future studies reporting on the adverse effects of β2-agonists should also stress the relevance of such findings within the context of current management guidelines.

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REFERENCES

To the Editor:

We thank Dr. D’Urzo for his interest in our article (CHEST 1995; 105:1235-39). We disagree with the concept that what happens in mild, well-controlled asthmatics would not be expected to occur in moderate or severe asthmatics. High-dose inhaled corticosteroid did not prevent the development of tolerance to the bronchoprotective effect of salbutamol vs methacholine nor did it prevent salbutamol-induced increased airway responsiveness to allergen.1 To specifically answer Dr. D’Urzo’s query regarding salmeterol, we have demonstrated identical findings in a group of eight asthmatics who required moderate to high doses of inhaled corticosteroids.2

To our knowledge, the only investigation that has failed to show tolerance to the bronchoprotective effect of inhaled β2-agonists is the article noted by Dr. D’Urzo by Booth et al (Thorax 1993; 48:1121-24) in which tolerance did not occur to the small bronchoprotective effect of salmeterol vs methacholine measured 12 h after the last dose. This may be the result of the study design since their subjects were allowed ad-lib use of “rescue” salbutamol at an unspecified rate. We have demonstrated3 that tolerance to the bronchoprotective effect of inhaled β2-agonists occurs at the low µg/dose of salbutamol 200 µg/d; therefore, failure to demonstrate tolerance in the study by Booth et al may, in fact, be because it was already present at the beginning of the study.

β2-agonist-induced tolerance to the bronchoprotective effect is not confined to mild asthmatics and is not inhibited by inhaled corticosteroids. We remain firm in our belief that the regular use of inhaled β2-agonists in asthmatics should be avoided if at all possible.

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